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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/185,904	11/03/1998	CHRISTEN M. ANDERSON	660088.420	1190

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EXAMINER
SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
1653	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/185,904	Applicant(s) ANDERSON ET AL.
	Examiner Holly Schnizer	Art Unit 1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42 and 44-101* is/are pending in the application.

4a) Of the above claim(s) *1-41 and 58-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *42 and 44-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 November 1998* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

Continued Prosecution Application

The request filed on January 18, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/185,904 is acceptable and a CPA has been established. An action on the CPA follows.

Status of the Claims

Claims 1-42 and 44-101 are pending. This application contains claims 1-41 and 58-101drawn to an invention non-elected without traverse in Paper No. 7. A complete reply to the final rejection should have included cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. No amendments or cancellations were filed with the CPA. Therefore, Claims 1-41 and 58-101 are withdrawn from consideration as being drawn to a non-elected invention and Claims 42 and 44-57 will be considered in this Office Action.

Drawings

The drawings are objected to for reasons cited in the Form PTO 948 attached to Paper No. 8. Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 42 and 44-57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. Applicant is referred to the interim guidelines on written description published December 21, 1999 in the Federal Register, Volume 64, Number 244, pp. 71427-71440 (available at www.uspto.gov) and the Examiner training Materials on Written Description also available at www.uspto.gov.

7. Claims 42 and 44-57, as amended in Paper No. 19, are genus claims. Claim 42 is directed to a genus of human adenine nucleotide translocator (ANT) proteins with the inherent properties of a polypeptide (binds ligands). Claim 44-46 are directed to the genus of human ANT isoforms or any variants or fragments thereof, Claims 47-51 are directed to a genus of human ANT fusion proteins, and 52-57 are drawn to the genus of animal ANT fusion proteins or any variants or fragments thereof.

In Paper No. 19, Applicants argue that the description of the claimed invention in the specification is sufficient to reasonably convey to a person having skill in the art that the applicants, at the time of filing, had possession of the claimed invention. Applicants concede that the prior art and instant application teach over 30 adenine nucleotide translocators (ANT) polypeptides from a variety of organisms, that some organisms have 2 to 3 isoforms of ANT polypeptide, and that the structure of the family is highly conserved. Applicants also concede that there are a number of known functional

properties shared among the species within the claimed genus. Applicants argue that the amended claims are now drawn to an isolated recombinantly produced human ANT polypeptide that localizes to mitochondrial membranes and is capable of binding an ANT ligand and that the specification describes three isoforms of the human ANT polypeptide.

Applicants' arguments have been considered but are not deemed to be persuasive for the following reasons.

The specification discloses one amino acid sequence for each of the human ANT isoforms, ANT1, ANT2, and ANT3. However, the specification does not teach any characteristics of the human ANT polypeptide that would distinguish if from ANT polypeptides of other species. Moreover, the specification has not taught characteristics of each of the isoforms such that, for example, one could distinguish an ANT1 sequence from that of ANT 2 or 3 or distinguish an ANT1 variant or fragment from that of an ANT 2 variant or ANT 3 variant. The specification does not teach when a polypeptide sequence ceases to be a human ANT polypeptide. For example, the specification does not teach how many amino acid changes can be made and in what positions in SEQ ID NO:31 (human ANT1) and still be considered a human ANT1 polypeptide. Allelic variation is a common occurrence and the specification does not provide any guidance regarding how much variation is allowed for the ANT polypeptide to still be considered human. Thus, it appears that the specification does not provide any common, distinguishing characteristics to describe the genus.

Claims 52-57 are drawn to the genus of any animal ANT proteins or fusion proteins. Again, the specification does provide any examples of an animal ANT polypeptide and not teach any characteristics of an animal ANT polypeptide that would distinguish if from ANT polypeptides of other species. Moreover, the specification has not taught characteristics of each of the isoforms such that, for example, one could distinguish one isoform from the next. The specification does not teach when a polypeptide sequence ceases to be an animal ANT polypeptide. For example, the specification does not teach how many amino acid changes can be made and in what of an animal ANT polypeptide sequence and still be considered an animal ANT polypeptide. Allelic variation is a common occurrence and the specification does not provide any guidance regarding how much variation is allowed for the ANT polypeptide to still be considered animal. Thus, it appears that the specification does not provide any common, distinguishing characteristics to describe the genus.

Claims 44-46 are drawn to an ANT1, ANT2, or ANT3 polypeptide, respectively, or variant or fragment thereof. The specification indicates that an ANT variant is a polynucleotide that encodes an analog having an insertion, deletion, or substitution (p. 18, entire page) and a "fragment" as any ANT polypeptide that retains "essentially the same biological function or activity" as an ANT polypeptide (sentence bridging pages 19-20). The specification and claim do not place any limit on the number of amino acid substitutions, deletions, and/or additions that may be made. Therefore, the scope of the claim includes variants and fragments of any length and sequence. The genus is highly variant because a significant number of structural differences between genus members

is permitted and the specification and claims do not indicate what distinguishing attributes are shared by the members of such a genus (see Examiner's Training Materials on Written Description, Example 13). The specification does not define when a protein ceases to be an ANT1, 2, or 3 polypeptide variant or fragment or even when a protein ceases to be any ANT polypeptide. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is extremely variant, then the three species, ANT 1, ANT 2, and ANT3 having the sequences defined by SEQ ID Nos: 31-33 alone are insufficient to describe the genus of any ANT 1, 2 or 3 protein having any sequence and any length. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, the disclosure is insufficient to show that one of skill in the art would conclude that applicant was in possession of the claimed genus.

The specification fails to provide an adequate written description as to what the common core/bond is that these human or, animal or, "fragments" and "variants" thereof must retain in order to remain within the respective ANT genus. Therefore, the rejection as stated in Paper No. 8 is maintained.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

2. Claims 42 and 44-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Marzo et al.(Science (Sept. 25, 1998) 281(5385): 2027-2031; ref. CC in IDS filed Sept. 8, 2000 as Paper No. 5).

3. As stated in Paper No. 8, Marzo et al. disclose a purified human ANT2 protein (p. 2029, Col. 1, lines 9-32, Fig. 2C, Fig. 4).). Applicants argument in Paper No. 19 that the polypeptides of Marzo et al. are not recombinant and are not capable of binding an ANT ligand, and that Marzo et al. do not disclose an isolated, recombinant human ANT polypeptide that is capable of binding an ANT ligand has been considered but is not deemed persuasive for the reasons given in the previous Office Actions (paper Nos. 8 and 15).

4. Marzo et al. state that ANT was purified to greater than 95% homogeneity and found to be uncontaminated by other proteins (see p. 2029, Col. 1, lines 29-31). Therefore, it appears that the polypeptide of Marzo et al. was isolated. ANT2 is considered a "variant" of ANT2 and ANT3 (and meets the limitations of clm. 44-46). Figure 4A shows the coimmunoprecipitation of Bax and ANT from a human cell line (see Fig. 4A and respective figure legend). A ligand is a molecule that binds to a macromolecule (in this case an ANT polypeptide). Therefore, the ANT polypeptide disclosed in Marzo et al. is considered to be "capable of binding an ANT ligand" which, in this case, is Bax (see Fig. 4). Thus, it appears that the ANT polypeptide of Marzo et al. is patentably indistinguishable from that of the present invention, even though it is produced and isolated by a different process than the present invention (co-

immunoprecipitation rather than recombinant techniques). The present claim is a product-by-process claim. In the instant case, the protein disclosed in Marzo et al. is an ANT polypeptide and therefore must have an ANT sequence, structure, and function. Where the claimed and prior art products are identical or substantially identical in structure or composition, as in the present case, a prima facie case of either anticipation or obviousness has been established. (see MPEP 2112.01 and In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) cited therein). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." (In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) as cited in MPEP 2112.01). The prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. (see MPEP 2112.01 and In re Best, 562 F.2d at 1255, 195 USPQ at 433. See also Titanium Metals Corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)). In the present case, there is no evidence that the ANT polypeptides of Marzo et al. are not the same. Therefore, the anticipation rejection over Marzo et al. is maintained.

5. Claims 42 and 44-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Fiore et al. (Biochimie (Feb. 1998) 80: 137-150; ref. BE of IDS filed Sept. 8, 2000 as Paper No. 5).

6. As stated in the Office action of Paper No. 8, Fiore et al. provide a review of mitochondrial ADP/ATP carrier proteins (also known as ANT proteins) and provides

evidence that ANT proteins are very well known in the art. Figure1 of the Fiore et al. reference provides an amino acid sequence alignment of known ANT proteins from human, bovine, mouse, rat, as well as other sources. In particular, the sequences of human ANT 1, 2 and 3 are provided. The Fiore et al. reference indicates that the ANT proteins from human and animal sources have not only been isolated but are also fairly well characterized. For example, Fiore et al. state "the definite characterization of the ADP/ATP carrier as a transport protein was established after reincorporation of the isolated carrier into liposomes and reconstitution of transport" (p. 138, Col. 1, last 4 lines of the column) and the beef heart ADP/ATP carrier isolated in the presence of detergent is able to undergo the transition between two conformational states (pl. 145, Col. 1, lines 1-9).

7. Applicants argument in Paper No. 19 that the Fiore et al. reference does not teach each and every limitation of the claim has been considered but is not deemed persuasive because Fiore et al. teach that isolation of beef heart ANT polypeptides was known in the art and animal ANT polypeptides are considered a "variant" of ANT1, 2, and/or 3 (again see p. 138, Col. 1, last 4 lines which state that an ANT (an ADP/ATP carrier) polypeptide was isolated). Moreover, any ANT polypeptide is considered a "variant" of an ANT 1, 2, and/or 3 polypeptide. Therefore, the disclosure in Fiore et al. of an isolated yeast ANT polypeptide (p. 144, last paragraph) is also considered to meet the limitations of the claims.

8. With respect to Claim 42, Applicant is reminded that the Claim is drawn to an "isolated" human ANT polypeptide. The specification does not define what amino acid

sequences are considered "human" ANT polypeptide sequences. Polypeptides are characterized by their amino acid sequences and the specification does not define any amino acid sequences or motifs or functional characteristics that are uniquely human and are not found as a variant in other species (for example, sequences that distinguish ANT polypeptides as being "human" rather than "animal"). Having only the knowledge of the ANT polypeptide sequence, the skilled artisan could only guess as to the species from which it was isolated. Moreover, an ANT polynucleotide could be isolated from human and modifications changing the amino acid sequence could be made that result in another "human" ANT polypeptide sequence (that of an modified human ANT polypeptide). This "human' ANT polypeptide could have the same sequence as an ANT polypeptide found in another species.

9. Therefore, without some distinguishing characteristic of what constitutes an isolated, "human" ANT polypeptide, the isolation of ANT polypeptides described in Fiore et al. is considered to meet the limitations of the claims.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 42 and 44-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fiore et al. (Biochimie (Feb. 1998) 80: 137-150; ref. BE of IDS filed Sept. 8, 2000 as Paper No. 5) in view of Rosenberg (Protein Analysis and Purification: Benchtop Techniques (1996) Birkhauser, Boston, pages 335-347; ref. CE of IDS filed Sept., 8, 2000 as Paper No. 5).

13. As stated in the Office action of Paper No. 8, the teachings of Fiore et al. have been described above. Fiore et al. teaches the full-length amino acid sequence of several human ANT polypeptides. Fiore et al. also disclose that a yeast strain containing an ANT carrying a polyhistidine tag at the C terminus was constructed to allow purification by immobilized metal ion affinity chromatography (p. 144, Col. 1, last paragraph). However, Fiore et al. do not teach a human or animal ANT fusion protein.

14. Rosenberg shows that it is standard in the art to construct fusions between a protein of interest and an enzyme (for example, β-galactosidase (β-Gal) (p. 336, lines 3-6 and section titled "Expression and Purification of lacZ and trpE Fusion Proteins") or an affinity tag (for example His-Tag or FLAG or GST (see p. 341-347)). Rosenberg teaches that using β-Gal as the fusion partner provides an advantage because

antibodies to β-Gal can be used to affinity purify the fusion protein and to follow purification of the fusion protein by Western blot analysis of the various fractions. Rosenberg also teaches that a protease cleavage site can easily be engineered into the fusion so that the fusion partner can be separated from the protein of interest after purification (see p. 344, Section 11.15).

15. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to express the well known human and animal ANT protein sequences taught in Fiore et al. as fusion proteins wherein the fusion partner was a polypeptide or enzyme having affinity for a ligand. One would have been motivated to do so because such a protein would allow easier purification on an affinity column. Using β-Gal as the fusion partner has the added benefit that the fusion protein can be easily monitored during purification (for optimization of purification conditions) or during expression (to localize the fusion protein in cells using the enzymatic activity of the β-Gal protein). Contrary to Applicant's assertions, one would have a reasonable expectation of success in expressing a human or animal ANT polypeptide as a fusion protein since Fiore et al. discloses that such as been done successfully with an ANT polypeptide that has high sequence homology to the human and animal ANT polypeptides.

16. In response to applicant's argument in Paper No. 19 that Fiore et al. or Rosenberg et al. individually does not contemplate recombinant expression of human ANT polypeptides capable of binding an ANT ligand, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of

references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With respect to Applicant's arguments in Paper No. 19, regarding secondary considerations: The arguments of counsel cannot take the place of evidence in the record. In re Schulze,

346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. (See MPEP 716.01(c) and MPEP § 2145 generally for case law pertinent to the consideration of applicant's rebuttal arguments.) In the present case, there is no evidence of a long felt need or any failure of others. In addition, the argument that the claimed subject matter solved a problem that was long standing in the art is not persuasive for the following reasons in addition to the reasons given above. There is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. Moreover, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem (see MPEP 716.04). Applicants appear to rely on Miroux et al. as evidence that a human ANT could not be isolated. This is not convincing. First, Miroux et al. show that the ANT polypeptides were overproduced in E. coli and this does not provide evidence

that ANT polypeptides could not be recombinantly produced in other organisms. On the contrary, Fiore et al. provides evidence of successful expression and isolation of ANT polypeptides in yeast (see p. 144, Col. 1, last paragraph). Second, contrary to Applicants assertions, expression of cloned eukaryotic genes in inclusion bodies in E. coli is a popular way of obtaining large amounts of protein. After isolating from inclusion bodies , the protein of interest is selectively solubilized. It is noted that Rosenberg et al. disclose a protocol for purification of proteins from inclusion bodies in E. coli (p. 339-340. Rosenberg et al. state that such purification is popular method of isolating proteins because it allows easy separation of the protein of interest from the majority of contaminants (p. 339). After inclusion bodies are isolated, they are washed and the protein of interest is solubilized. Thus, Rosenberg et al. provides evidence that the skilled artisan had the knowledge to isolate functional proteins from inclusion bodies. Applicants have not provided any evidence that one of skill in the art could not isolate a functional ANT polypeptide from the inclusion bodies disclosed in Miroux et al.

Thus, for the reasons described above, the rejection is maintained.

17. Claims 42 and 44-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adrian et al. (Mol. Cell Biol. (1986) 6(2): 626-634) in view of Fiore et al. (Biochimie (Feb. 1998) 80: 137-150; ref. BE of IDS filed Sept. 8, 2000 as Paper No. 5).

In the previous Office Actions, claims 42, 51, and 56-57 were mistakenly omitted. Due to this error, this Office Action will not be made final. These additional claims should have been included for the reasons cited in the previous Office Action and

below. In addition, in Claims 51 and 56-57, it is noted that all polypeptide sequences are cleavable by some type of protease. In Claim 57, the Histidine tag of the fusion protein disclosed in Fiore et al. (p. 144, Col. 1, last paragraph) has an affinity to a ligand (metal ions). Thus, for the reasons cited below and in the previous Office action, Claims 42 and 44-57 appear to be obvious over the prior art.

As stated in the Office Action of Paper No. 8, Adrian et al. disclose the expression of fusion proteins comprising *Saccharomyces cerevisiae* ADP/ATP translocator (ANT) proteins of various lengths (see p. 631, Fig. 5) and the enzyme β-Galactosidase in an investigation of what amino acids are important in targeting the protein to the mitochondrial membrane. The study reveals that several of the fusion proteins were delivered to the mitochondria (see p. 630, Col. 2, lines 23-30; and p. 631, Table 1). Furthermore, it appears that the ANT polypeptide of Adrian et al. are capable of binding ANT ligands (see Fig. 6).

18. Adrian et al. do not teach that the ANT proteins were derived from human or animal sources.

19. As described above, Fiore et al. disclose the amino acid sequence alignment of 29 sequences of known ANT proteins from human and animal sources, and indicate that these proteins have been isolated (p. 145, Col. 1, lines 1-9). The amino acid sequences of several human ANT polypeptides are disclosed (see Fig. 1). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to express the human and animal ANT proteins described in Fiore et al. as fusion proteins as taught in Adrian et al. One having ordinary skill in the art would have

been motivated to substitute human or animal ANT instead of the disclosed yeast ANT in order to study the mitochondrial localization sequences in human and animal ANT. Characterization of animal and more importantly human ANT proteins is essential to the development of diagnostic and treatment tools because as taught in Fiore et al. (p. 146, Col. 2), these proteins have a central role in cellular energy metabolism and it is likely that dysfunction of these proteins is involved in mitochondrial disorders. One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in isolating human or animal ANT polypeptides using the method of Adrian et al. given the high homology of the sequences between sequences and the success of expressing a yeast ANT fusion polypeptide as described in Adrian et al.

In response to applicant's argument in Paper No. 19, that Adrian et al. individually does not contemplate recombinant expression of human ANT polypeptides capable of binding an ANT ligand, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument (Paper No. 19) that the motivation for combining the references given in the previous Office Action is beside the point because Adrian et al. is concerned only with subcellular localization targeting motifs while the present invention is not so limited is not persuasive. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences

would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicants reference to Miroux et al. (Paper No. 19) as evidence of the inability to prepare ANT polypeptides is not convincing since Miroux et al. state that the ADP/ATP carrier from mitochondria was overproduced (see line 20-22). Moreover, Adrien et al. Show that recombinant expression of ANT is successful. In addition, Fiore et al. state (p. 143, Col. 1, lines 2-7 of section titled "Transcriptional Regulation and tissue specificity) and applicants admit (last 4 lines on p. 4 of Response filed Nov. 5, 2001, Paper No. 12) that the sequences of ANT from different species are highly homologous. Therefore, absent evidence that those skilled in the art could not isolate the human ANT polypeptide, it appears that one of skill in the art would have a high expectation of success in practicing the method of Adrian et al. using the human ANT sequence since Adrian et al. teaches the successful expression and isolation of a highly homologous ANT polypeptide.

With respect to Applicant's arguments regarding secondary considerations (Paper No. 19): The arguments of counsel cannot take the place of evidence in the record. In re Schulze,

346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the

disclosed subject matter from the applicant. (See MPEP 716.01(c) and MPEP § 2145 generally for case law pertinent to the consideration of applicant's rebuttal arguments.) In the present case, there is no evidence of a long felt need or any failure of others.

In addition, the argument that the claimed subject matter solved a problem that was long standing in the art is not persuasive for the following reasons in addition to the reasons given above. There is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. Moreover, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem (see MPEP 716.04). Applicants appear to rely on Miroux et al. as evidence that a human ANT could not be isolated. This is not convincing. First, Miroux et al. show that the ANT polypeptides were overproduced in E. coli and this does not provide evidence that ANT polypeptides could not be recombinantly produced in other organisms. On the contrary, Adrian et al. provides evidence of successful expression and isolation of ANT polypeptides in S. cerevisiae (see Fig. 6 for an example of an ANT polypeptide that localizes to the mitochondria and that binds an "ANT ligand" (an ANT antibody). Second, contrary to Applicants assertions, expression of cloned eukaryotic genes in inclusion bodies in E. coli is a popular way of obtaining large amounts of protein. After isolating from inclusion bodies , the protein of interest is selectively solubilized. Applicants have not provided any evidence that one of skill in the art could not isolate a functional ANT polypeptide from the inclusion bodies disclosed in Miroux et al. With respect to Applicants argument that the method of recombinantly producing an ANT

polypeptide was needed in the art is not convincing since the claimed subject matter is directed to a polypeptide and not a method. Thus, the rejection is maintained.

Double Patenting

20. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

21. Claims 42 and 46-57 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 42, 46, 47, 48, 51, 52, 53, 56, and 57 of copending Application No. 09/393,441. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Mon. & Thurs., 8am-5:30pm and Tues. & Wed. 9-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
April 8, 2002

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